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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/800,362	PARDRIDGE ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *18-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-17) and EGFR as the target sequence from claim 2, in the reply filed on 12/09/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 18-32 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Objections

2. Claim 4 is objected to because of the following informalities: Claim 4 ends with a ".", which is underlined text and appears to be an amendment to the instant claim. However, the claim is not indicated as amended. Appropriate correction is required.

3. Claim 5 is objected to because of the following informalities: Claim 5 does not end with a period. Appropriate correction is required.

4. Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 17 is drawn to a composition according to claim 16 and requires that the cell to which the shRNA gene is to be delivered is located within an animal. However, the claim depends from a composition claim and a limitation placed on the location of a cell to which the composition is intended to be administered is not a further limitation on the composition itself. The composition of claim 17 is therefore the same composition as set forth in claim 16.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 3-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites, "said human epidermal growth factor receptor mRNA comprising a nucleotide sequence having numbered nucleotides from 1 to 5532." However, the skilled artisan cannot determine the metes and bounds of what is being claimed with this terminology, without assumption, because no context is provided in the claim for determining what would constitute a nucleotide sequence having numbered nucleotides or what those particular numbers may refer to.

Claim 4 recites, "a nucleotide sequence that is antisense to a portion of said human epidermal growth factor receptor mRNA that is located between numbered nucleotides 2300and 3800." However, the skilled artisan cannot

determine the metes and bounds of what is being claimed with this terminology, without assumption, because no context is provided in the claim for determining what would constitute a nucleotide sequence that is antisense to a portion of an mRNA between numbered nucleotides numbered nucleotides 2300 and 3800 or what those particular numbers may refer to. It is noted that a space should appear between "2300" and "and."

Claim 5 recites, "wherein said portion of said human epidermal growth factor receptor mRNA that is located between numbered nucleotides 2500 and 3000." However, the skilled artisan cannot determine the metes and bounds of what is being claimed with this terminology, without assumption, because no context is provided in the claim for determining what would constitute a portion of said human epidermal growth factor receptor mRNA that is located between numbered nucleotides 2500 and 3000 or what those particular numbers may refer to.

Claim 6 recites, "wherein said portion of said human epidermal growth factor receptor mRNA that is located between numbered nucleotides 2500 and 2600." However, the skilled artisan cannot determine the metes and bounds of what is being claimed with this terminology, without assumption, because no context is provided in the claim for determining what would constitute a portion of said human epidermal growth factor receptor mRNA that is located between numbered nucleotides 2500 and 2600 or what those particular numbers may refer to.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The invention set forth in claims 1 -17 is broadly drawn to a receptor specific nanocontainer comprising a liposome, a gene comprising sufficient genetic information to encode a short hairpin RNA (shRNA), a plurality of receptor targeting agents and a plurality of conjugation agents the targeting agents to the liposome. Dependent claims require that the shRNA be antisense to human epidermal growth factor, comprise particular sequences having specified "numbered nucleotides (see above)," that the nanocontainers be of a specific diameter, have a specified number of targeting agents that are capable of targeting a receptor on a solid tumor, have a specified number and identity of conjugation agents of a specified molecular weight range and that the claimed nanocontainer is comprised with a pharmaceutically acceptable carrier.

Instant claims 1-11, and 16-17 read broadly on a large genus of "genes" that comprise a sufficient amount of genetic information to encode an shRNA wherein the gene can be any "gene" and therefore must comprise all the

elements known to be associated with a complete gene. In particular, the terminology, "a gene comprising a sufficient amount of genetic information to encode an shRNA", is not used as known in the art and reads on all the components required by genes including, at least, promoter and enhancer elements, 5' and 3' UTR regions, introns and exons and any other distal or proximal, cis or trans acting elements required for the expression of that "gene." Claims 2-6 require that the shRNA encoded by the gene comprises a nucleotide sequence that is antisense to at least a portion of EGFR wherein the EGFR mRNA comprises "numbered nucleotides" (claims 4-6).

The specification provides only a general disclosure of what is encompassed by this terminology wherein it states, "The gene includes a sufficient amount of genetic information to encode a short hairpin RNA. The nucleotide sequence of the short hairpin RNA includes nucleotides that are antisense to at least a portion of mRNA or other nucleotide sequence that is necessary for the receptor-targeted cell to function"(section 0023). The specification provides no definition of " a gene encoding sufficient information to encode a shRNA" and no examples of genes that comprise sufficient information to encode shRNAs, wherein those shRNAs function, commensurate with the breadth of what is claimed, to inhibit gene expression. The species disclosed are plasmid DNAs that comprise nucleotide sequences that encode shRNAs, which, when expressed, target and modulate the expression of a single gene, the human EGFR gene.

Therefore, the general disclosure of the specification does not provide an adequate written description of the claimed invention, commensurate with the breadth of what is claimed, because the specification does not provide an adequate written description of the claimed "gene" that can be any "gene" that comprises sufficient genetic information to encode an shRNA. The specification does not provide a correlation between the structure of the claimed "gene" and the function of encoding an shRNA and has not disclosed any distinguishing identifying characteristics of the broad genus of claimed "genes" that would indicate that Applicant was in possession of what is now claimed.

The specification does not provide an adequate written description of the claimed invention and state of the art cannot provide this description, as evidenced by the Online Medical Dictionary, viewed 2/28/2006, which indicates that a gene is a unit of inheritance occupying a specific locus on a chromosome, can be of different allelic forms, can be a split gene and may be best defined as a sequence of nucleotides that are required to produce a single polypeptide (see attached web page/ search results). No definition of an RNA gene was found in the Online Medical Dictionary (see attached web page/search results). Therefore, in recognizing that a gene is a sequence of nucleotides best defined as those required to produce a polypeptide, the state of the art does not provide a description that is sufficient to allow the skilled artisan to immediately recognize that applicant was in possession of the instantly claimed invention, a receptor specific nanocontainer that comprises a "gene," for example.

MPEP § 2163[R-2] I. states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003);< Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.
>
> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117.
>
> Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").
>
> An applicant may also show that an invention is complete by disclosure of sufficiently
> detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the invention now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of a representative number of species of the claimed genes that comprise a sufficient amount of genetic information to encode an shRNA, commensurate with the breadth of what is claimed. Additionally, Applicant has not adequately described any distinguishing identifying characteristics of the above receptor specific

nanocontainers that comprise "genes" that would be sufficient to show that the applicant was in possession of the instant invention, commensurate wit the breadth of what is claimed.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. In the instant case, although claims 3-6 are considered indefinite for the reasons above, a reasonable interpretation considers that any mRNA encoding EGFR will have the required numbered nucleotides. The following prior art is applied.

11. Claims 1, 7, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Talke et al. (US 5,891,689).

The invention set forth in claims 1, 7, 16 and 17 is drawn to a receptor specific nanocontainer comprising a liposome, a gene comprising sufficient genetic information to encode a short hairpin RNA (shRNA), a plurality of receptor targeting agents and a plurality of conjugation agents connecting each targeting agent to the exterior surface of the liposome wherein the claimed receptor specific nanocontainer is a specific diameter and a composition comprising the receptor specific nanocontainer and a pharmaceutically acceptable carrier.

Talke et al. disclose and claim microparticles that have a diameter of 100 nanometers that can be liposomes that comprise heme receptor targeting agents conjugated to the exterior of the liposomes and plasmid DNA encapsulated within the interior of the liposome and that the liposomes of their invention are comprised with pharmaceutically acceptable carriers (col. 1, lines 25-40; col. 6, line 35 to col. 7, line 12; col. 8 and example 3). The disclosure of Talke et al., of plasmid DNA that is encapsulated in the interior of the liposomes of their invention is reasonably considered to read on a gene comprising sufficient genetic information to encode a short hairpin RNA (shRNA) because, as written, the claim does not require that the gene express an shRNA, only that it comprises sufficient genetic information to encode a short hairpin RNA.

Therefore, Talke et al. anticipate the instant invention as set forth in claims 1, 7, 16 and 17.

12. Claims 1 and 7-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhang et al. 2003 (Reference cited on the PTO Form 1449 filed 9/7/2004).

The invention set forth in claims 1, 7 and 16-17 is relied upon as above. Dependent claims 8-15 require that the claimed receptor specific nanocontainer have a specified number of targeting agents that are capable of targeting a receptor on a solid tumor that is one of the solid tumors listed in claim 13 or that is a brain tumor (claims 8, 12-14) wherein the targeting agent is capable of targeting one of the receptors as listed in claim 15, wherein the conjugation agent is polyethylene glycol, sphingomyelin or organic polymers, the MW of the conjugation agent is 1000-50,000 daltons and the number of conjugation agents conjugated to the liposome is from 100 to 10,000 (claims 9-11).

Zhang et al. disclose the in vivo knockdown of gene expression in brain cancer in adult rats using 85 nm pegylated immunoliposomes (PILs) to deliver shRNA expression plasmids to solid tumors that are brain tumors in the animals (abstract). The surface of the PILs disclosed by Zhang et al. is conjugated with several thousand strands of 2000 Da PEG and the tips of 1-2% of the PEG strands are tethered with a targeting ligand which can be a peptidomimetic monoclonal antibody that binds the rat transferrin receptor, which is a disclosure of about 200 PEG strands that are tethered with a targeting ligand ((1%) x (2000)) (pg. 1040, col. 1 and Fig. 1; pg. 1041, materials and methods). The PILs disclosed by Zhang et al. are disclosed as encapsulating plasmid constructs that express shRNAs, which is reasonably considered to read on a receptor specific

nanocontainer that comprises "a gene comprising a sufficient amount of genetic information to encode a short hairpin RNA, said gene being located within the internal compartment of the liposome," as claimed. Zhang et al. disclose that the transferrin targeted PILs used in their method successfully inhibit luciferase gene expression in intercranial brain cancer that was developed in rats using C6 rat glioma cells that were permanently transfected with the gene encoding luciferase, which is reasonably considered a disclosure of a targeting agent that is capable of targeting a receptor on a solid tumor.

Therefore, Zhang et al. anticipate the instant invention as set forth in claims 1 and 7-17.

13. Claims 1-13 and 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by McSwiggen et al. (US 2004/0192626 A1). The invention set forth in claims 1 and 7-17 is relied upon as above. Dependent claims 2-6 require that the shRNA comprises a nucleotide sequence that is antisense to at least a portion of mRNA from human epidermal growth factor receptor (EGFR; aka. HER1) wherein the mRNA has certain "numbered nucleotides."

McSwiggen et al. disclose RNA interference mediated inhibition of human epidermal growth factor receptor (EGFR, aka. HER1 – see Table 1) using shRNAs that can be expressed from plasmids comprised in liposomes (Abstract, pg. 3, pg. 25, section 0189; pg. 207, section 0204). McSwiggen et al. disclose that immunoliposomes can be used to deliver the shRNAs of their invention to hematopoietic cells and Lewis lung cell carcinoma cells, liposomes that

incorporate PEG, liposomes that are used for delivery to localize the shRNAs of the invention to certain tissue types and targeting agents that are capable of targeting cell receptors (pg. 64, sections 0565-0572 including the incorporation of references therein; pgs. 72-74) The disclosure of immunoliposomes is considered an inherent disclosure of liposomes that are less than 200 nm, comprise between 5-500 receptor targeting agents conjugated to the liposome by 100-10,000 PEG conjugation agents wherein the PEG is between has a molecular weight of 1000 and 50,000 Daltons (as evidenced by Zhang et al. 2002, J. Gene Med. Vol. 4: pp. 183-194 who disclose immunoliposomes for the delivery of plasmids expressing antisense nucleotide sequences to cells having receptors) and the targeting agents are capable of targeting a receptor on a solid tumor and wherein the targeting agent is capable of targeting the transferrin receptor (disclosed in the incorporated references, section 0572).

Therefore, McSwiggen et al. anticipate the instant invention as set forth in claims 1-13 and 15-17.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. 2002 (Reference cited on the PTO Form 1449 filed 9/7/2004), Shi et al. 2001 (PNAS Vol. 98(22): pp. 12754-12759) and Paddison et al. (Reference cited on the PTO Form 1449 filed 9/7/2004).

The invention set forth in claims 1-17 is drawn to a receptor specific nanocontainer comprising a liposome, a gene comprising sufficient genetic information to encode a short hairpin RNA (shRNA), a plurality of receptor targeting agents and a plurality of conjugation agents connecting each targeting agent to the exterior surface of the liposome (claim 1). Dependent claims 2-6 require that the shRNA comprises a nucleotide sequence that is antisense to at least a portion of mRNA from human epidermal growth factor receptor (EGFR; aka. HER1) wherein the mRNA has certain "numbered nucleotides." Dependent claims 7-17 require that the claimed receptor specific nanocontainer be of a

specific diameter (claim 7), have a specified number of targeting agents that are capable of targeting a receptor on a solid tumor that is one of the solid tumors listed in claim 13 or that is a brain tumor (claims 8, 12-14) wherein the targeting agent is capable of targeting one of the receptors as listed in claim 15, wherein the conjugation agent is polyethylene glycol, sphingomyelin or organic polymers, the MW of the conjugation agent is 1000-50,000 daltons and the number of conjugation agents conjugated to the liposome is from 100 to 10,000 (claims 9-11), and wherein the receptor specific nanocontainer is comprised with a pharmaceutically acceptable carrier (claims 16 and 17).

Zhang et al. teach the receptor mediated delivery of a plasmid that expresses an antisense nucleotide sequence that is complementary to nucleotides 2317-3006 of the human EGFR mRNA and that inhibits the expression of EGFR to human brain cancer cells using pegylated immunoliposomes (pg. 192, col. 2; pg. 183). Zhang et al. teach the inhibition of human EGFR gene expression in brain cancer cells (human glioma) using 85 nm pegylated immunoliposomes (PILs) to deliver antisense expression plasmids to brain tumors wherein the PILs encapsulate the expression plasmids, the surface of the PILs is conjugated with several thousand strands of 2000 Da PEG, the tips of 1-2% of the PEG strands are tethered with a targeting ligand which can be a peptidomimetic monoclonal antibody that binds the rat transferrin receptor or human insulin receptor, which is a disclosure of about 200 PEG strands that are tethered with a targeting ligand ((1%) x (2000)) (pg. 184, cols. 1-2). The PILs taught by Zhang et al. encapsulate plasmid constructs that comprise promoters,

which plasmid constructs are reasonably considered to read on "a gene comprising a sufficient amount of genetic information to encode a short hairpin RNA, said gene being located within the internal compartment of the liposome," as claimed. Zhang et al. teach that the receptor targeted PILs used in their method successfully inhibit hEGFR gene expression in brain cancer cells and that PILs provide a new approach to gene targeting that is effective in vivo following intravenous administration without viral vectors (abstract). Zhang et al. teach that, "The PIL gene targeting technology allows for widespread gene expression in the brain in vivo following the intravenous injection of non-viral gene formulations" (pg. 193, col. 1). Zhang et al. teach that the expression of therapeutic genes may be restricted to brain cancer in vivo following intravenous administration of the exogenous gene with the combined us of tumor specific gene promoters and the gene targeting technology using PILs" (pg. 193, col. 2).

Zhang et al. do not teach shRNAs that comprise a nucleotide sequence that is antisense to at least a portion of human EGFR mRNA.

Shi et al. teach that brain specific expression of an exogenous gene in mice using PILs to deliver plasmids encoding an exogenous gene to the brains of mice following intravenous injection wherein the PILS are 85 nm pegylated immunoliposomes, the surface of the PILs is conjugated with several thousand strands of 2000 Da PEG and the tips of 1-2% of the PEG strands are tethered with a targeting ligand that is an antibody that binds the rat transferrin receptor (pg. 12754, col. 2). Shi et al. teach that it is possible with the combined use of a brain specific promoter and a gene targeting system using PILS and that this

gene delivery system offers the same advantages of viral delivery systems such as interiorization of the exogenous gene in an nanocontainer, protection from endonucleases in vivo and provides surface proteins that trigger uptake of the gene by target cells (pg. 12758, col. 2).

Paddison et al. teach the inhibition of gene expression using shRNAs that are expressed from plasmid constructs in mammalian cells. Paddison et al. teach structural requirements for plasmids that express shRNAs in mammalian cells and that short hairpin RNAs can induce sequence specific gene silencing in mammalian cells by endogenous expression of shRNAs in cells (pg. 949, col. 2). Paddison et al. teach that the ability to encode a constitutive silencing signal may permit the marriage of shRNA induced silencing with in vivo and ex vivo gene delivery methods for therapeutic approaches based on stable RNAi in humans (pg. 956, col. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to make an 85 nm pegylated immunoliposomes that comprised several thousand strands of 2000 Da PEG wherein the tips of 1-2% of the PEG strands were tethered with an antibody that binds the transferrin receptor wherein the immunoliposomes comprised, in its interior, an expression plasmid that expressed an exogenous gene, wherein the immunoliposome was targeted to a brain tumor cell (as taught by Zhang et al. and Shi et al.) and the exogenous gene was an shRNA targeted to EGFR because Zhang et al. teach plasmids that express antisense nucleic acids that inhibit the expression of EGFR and that the receptor targeted PILs used in their

method successfully inhibit EGFR gene expression in brain cancer cells, providing a new approach to gene targeting that is effective in vivo following intravenous administration without viral vectors. Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, because Paddison et al. teach the structural requirements for plasmids that express shRNAs in mammalian cells and that shRNAs can induce sequence specific gene silencing in mammalian cells by endogenous expression from plasmids.

One of ordinary skill in the art would have been motivated to make 85 nm pegylated immunoliposomes that comprised several thousand strands of 2000 Da PEG wherein the tips of 1-2% of the PEG strands were tethered with an antibody that binds the rat transferrin receptor wherein the immunoliposome comprised, in its interior, an expression plasmid that expressed an exogenous gene, wherein the immunoliposome was targeted to a brain tumor cell (as taught by Zhang et al. and Shi et al.) and the exogenous gene was an shRNA targeted to EGFR because PILs as above, that comprised plasmids that expressed antisense nucleic acids to EGFR were known in the art (as taught by Zhang et al.), because the combined use of a brain specific promoter and a gene targeting system using PILs as a gene delivery system offers the same advantages of viral delivery systems such as interiorization of the exogenous gene in an nanocontainer, protection from endonucleases in vivo and provides surface proteins that trigger uptake of the gene by target cells (as taught by Shi et al.) and because the structural requirements for plasmids that express shRNAs in

mammalian cells wherein the shRNAs are effective inhibitors of target gene expression, was known in the art (as taught by Paddison et al.).

One of ordinary skill in the art would have expected success in making 85 nm pegylated immunoliposomes that comprised several thousand strands of 2000 Da PEG wherein the tips of 1-2% of the PEG strands were tethered with an antibody that binds the rat transferrin receptor wherein the immunoliposome comprised, in its interior, an expression plasmid that expressed an exogenous gene, wherein the immunoliposome was targeted to a brain tumor cell and the exogenous gene was an shRNA targeted to EGFR because PILs as above, that comprised plasmids that expressed antisense nucleic acids to EGFR were known in the art (as taught by Zhang et al.), because the combined use of a brain specific promoter and a gene targeting system using PILs as a gene delivery system offers the same advantages of viral delivery systems such as interiorization of the exogenous gene in an nanocontainer, protection from endonucleases in vivo and provides surface proteins that trigger uptake of the gene by target cells (as taught by Shi et al.) and because the structural requirements for plasmids that express shRNAs in mammalian cells wherein the shRNAs are effective inhibitors of target gene expression, was known in the art (as taught by Paddison et al.).

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

17. No claims are allowed.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own

application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER